The Seveso Studies on Early and Long-Term Effects of Dioxin Exposure: A Review

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The industrial accident that occurred in the town of Seveso, Italy, in 1976 exposed a large population to substantial amounts of relatively pure 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Extensive monitoring of soil levels and measurements of a limited number of human blood samples allowed classification of the exposed population into three categories, A (highest exposure), B (median exposure), and R (lowest exposure). Early health investigations including liver function, immune function, neurologic impairment, and reproductive effects yielded inconclusive results. Chloracne (nearly 200 cases with a definite exposure dependence) was the only effect established with certainty. Long-term studies were conducted using the large population living in the surrounding noncontaminated territory as reference. An excess mortality from cardiovascular and respiratory diseases was uncovered, possibly related to the psychosocial consequences of the accident in addition to the chemical contamination. An excess of diabetes cases was also found. Results of cancer incidence and mortality follow-up showed an increased occurrence of cancer of the gastrointestinal sites and of the lymphatic and hematopoietic tissue. Experimental and epidemiologic data as well as mechanistic knowledge support the hypothesis that the observed cancer excesses are associated with dioxin exposure. Results cannot be viewed as conclusive. The study is continuing in an attempt to overcome the existing limitations (few individual exposure data, short latency period, and small population size for certain cancer types) and to explore new research paths (e.g., differences in individual susceptibility). — *Environ Health Perspect* 106(Suppl 2):625–633 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-2/625-633bertazzi/abstract.html*

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Introduction

The accident that occurred in a chemical plant near the town of Seveso, Italy, in 1976 caused a large population to be exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin). An uncontrolled exothermic reaction during the manufacture of trichlorophenol produced the sudden release of a cloud of chemical substances that gave immediate signs of hazard: vegetation, birds, and courtyard animals were seriously affected; people who happened to be on the deposition path of the cloud developed nausea, headache, and eye irritation, and a few children were admitted to the local community hospitals for skin lesions on exposed parts of the body (*1*).

The presence of TCDD as the main component of the toxic cloud was made known 10 days after the accident. Fear for the health of local residents was justified by the known high toxicity of TCDD in animals and its ability to cause cancer under experimental conditions (*2*). Little was known at that time about its effects on human beings, especially after environmental exposure (*3*).

In the emergency situation after the accident, local health authorities were confronted with three main problems: ascertaining the nature and characteristics of the exposure, the extent of contamination, and the number of people involved; managing the risk with preventive measures for people and the environment; and planning and conducting health surveillance programs.

Exposure

Environmental Indicators

The amount of TCDD released in the Seveso accident has been the subject of conflicting estimates. The latest reevaluation (*4*), for example, concluded that this amount should be estimated at 34 kg or higher, whereas previous estimates (*5*) reported quantities from hundreds of grams to a few kilograms.

To ascertain the level of exposure and extent of contamination as well as the behavior and fate of TCDD in the environment, an extensive environmental monitoring program was carried out (*6*).

Soil monitoring was repeatedly performed between 1976 and 1986. Thousands of soil samples were analyzed, which allowed territorial mapping of TCDD distribution and of its behavior over time (*6,7*). Based on these measurements, three zones with decreasing TCDD levels were identified (Figure 1). Zone A, the most heavily contaminated area, had mean soil levels of TCDD ranging from 15.5 to 580 $\mu g/m^2$. In zone B the levels of TCDD did not exceed 5 $\mu g/m^2$ on average. A third area with lower contamination levels was defined and referred to as the zone of respect or zone R; here TCDD levels generally were below 1.5 $\mu g/m^2$.

Soil analyses also indicated that 2,3,7,8-TCDD accounted for over 90% of total dioxins in the environment, and that other isomers were present such as 1,3,7,8-TCDD in zone A and inside the plant and 1,3,6,8-TCDD and 1,3,7,9-TCDD in zone R (*8*). The actual source of these isomers was only hypothesized; in any case the amount compared to 2,3,7,8-TCDD was in practice irrelevant.

Investigations of deeper soil layers showed that the vertical gradient varied only slightly with time. Over 90% of

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Abbreviations used: CI, confidence interval; CIHD, chronic ischemic heart disease; COPD, chronic obstructive pulmonary disease; ppt, parts per trillion; RR, relative risk; SD, standard deviation; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

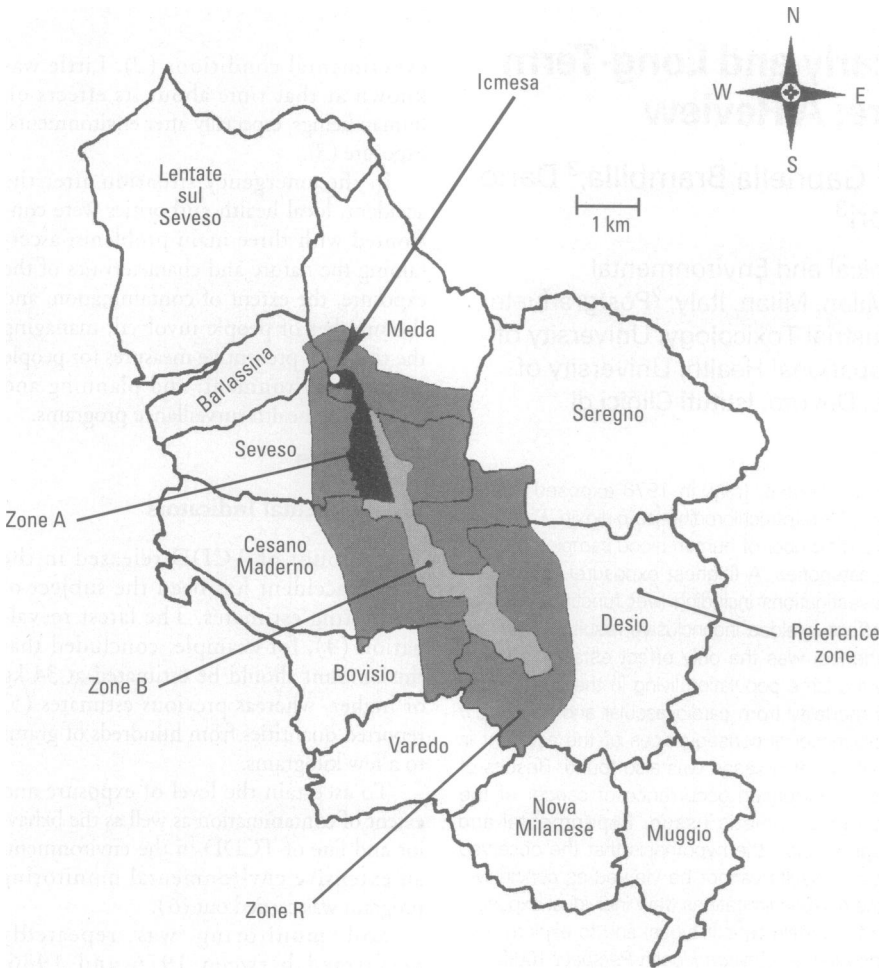

Figure 1. Map of the Seveso accident area showing the trichlorophenol plant, Icmesa, where the TCDD exposure occurred, the three contamination zones, A, B, and R, and the surrounding noncontaminated area adopted as a reference zone.

detectable TCDD was found in the thick upper 15-cm layer in 1977, and no further significant changes were observed after that time (*7*). This information guided all the reclamation processes. In zone A the entire top soil layer (at least 25 cm) was removed and the area covered with fresh uncontaminated soil. Rehabilitation of zone B entailed soil removal in public and private gardens only, whereas in the remaining territory the top soil underwent treatments such as plowing, harrowing, and sowing to dilute surface TCDD and help in its dispersal (*9*). TCDD levels in ground and surface water and in sediment showed consistently negative results that confirmed the low solubility of TCDD (*6*).

Airborne dust was monitored to evaluate the possibility that TCDD-containing particles were airborne from the contaminated soils, particularly during the reclamation works; both dustfall jars and high volume samplers were used. TCDD was found in 15 of 19 sediment specimens sampled in the part of zone A nearest to the plant where the accident took place. Values ranged from 0.06 to 2.1 ng of TCDD/g of dust for dustfall jar specimens and 0.17 to 0.50 ng of TCDD/g of dust for samples from high-volume samplers. Maximum TCDD fallout deposits occurred at the beginning of the summer and decreased with increasing distance from the plant (*10*).

TCDD levels in vegetation rapidly decreased as distance from the factory increased (*6*). Immediately after the accident, TCDD levels reached values up to several milligrams/kilogram, while in new vegetation that grew in the years following the accident TCDD levels dropped by several orders of magnitude (*11*).

Shortly after the accident an outbreak of animal deaths, mainly rabbits and poultry, was noted (*12*). Table 1 reports rabbit mortality in the three contaminated zones. Mortality in zone A was highest. Interestingly, a mortality rate close to 100% was noted on farms where animals were fed green fodder from contaminated areas, whereas a much lower mortality rate was observed on farms where animals were fed commercial feed or fodder collected either before the accident or far away from the plant where the accident took place. Data from autopsied animals showed that mean TCDD levels in rabbit livers were similar for zones A and B, whereas rabbits in zone R had lower levels although they were higher than the background (*12*). Measurements of TCDD in cows' milk also confirmed that higher levels were present in milk samples from farms close to the plant (*13*).

Human Indicators

Early signs such as skin lesions and in particular chloracne were markers to identify people most probably exposed to TCDD (*14*). By April 1977, 187 cases of overt chloracne had been diagnosed by an expert panel. Of these, 164 (88%) were children (*15*). The distribution of cases among children is shown in Table 2. The highest prevalence by far was seen in zone A, particularly near the plant, where contamination was maximal. The proportion of chloracne cases detected in a suburb called Polo, located in zone R, is noteworthy. This is probably the most obvious indication of exposure zone misclassification.

After the accident thousands of blood samples were collected and properly stored by Mocarelli et al. (*16*). At that time no methods were available to measure low dioxin concentrations in small blood samples, but such methods were developed in the 1980s. Results of the first measurements showed TCDD serum levels ranging from 828 to 56,000 ppt in 10 children with chloracne from zone A. Nine adults without chloracne, from the same area, had values ranging from 1770 to 10,400 ppt. Results of additional measurements recently have been reported. In subjects older than 13 years residing in the reportedly most polluted parts of the three exposure zones, the estimated median TCDD levels were 443 ppt (zone A, 177 subjects), 87 ppt (zone B, 54 subjects), and 15 ppt (zone R, 17 subjects), respectively (*17*). Additional blood samples were collected in 1992 and 1993 in a limited number of randomly selected subjects older than 20 years of age (*18*): preliminary results are available (*19*). Current lipid-adjusted

Table 1. Estimated rabbit mortality in the Seveso accident area, July to August 1976.

Contamination zone	Rabbits, estimated no.	Observed deaths, no.	Mortality, %
A, High exposure	1089	348	31.9
B, Medium exposure	4814	426	8.8
R, Low exposure	18,982	1288	6.8

Data adapted from Fanelli et al. (*13*).

Table 2. Distribution of chloracne cases diagnosed in children 3 to 14 years of age in an 8-month period following the Seveso accident.[a]

Contamination zone	Total population	Chloracne cases, no.	Prevalence, %
A	214	42	19.6
Max[b]	54	26	48.1
B	1468	8	0.5
R	8680	63	0.7
Polo[c]	750	19	2.5
Reference	48,263	51	0.1

[a]Data adapted from Caramaschi et al. (*15*). [b]Part of zone A closest to the factory. [c]Part of zone R closest to the factory.

TCDD values were backcalculated to the date of the accident using an estimated half-life of 7.1 years (*20*). In zone A (six subjects) the extrapolated mean value was 333.8 ppt, with standard deviation (SD) of 163.2 ppt and median of 388.7 ppt; in zone B (52 subjects) the mean was 111.4 ppt, SD of 83.6 ppt and median of 76.6 ppt. In 52 subjects of the referent population, the measured mean value was 5.3 ppt, SD 4.0 ppt and median 5.5 ppt. Interestingly, these serum measurements seem to confirm the zone categorization based on TCDD soil measurements. Blood measurements are available also for six subjects who moved into zone B after reclamation work was completed. Their mean TCDD level was 15 ppt, with a range from 6.8 to 46 ppt (*21*).

Few data exist on other human tissues. Measurements of TCDD in the adipose tissue at autopsy were done on two subjects. A 55-year-old woman who died from pancreatic cancer 7 months after the accident and was known to have suffered heavy exposure in zone A had TCDD concentration in the adipose tissue of 1840 ppt (*22*). A much lower level (10 ppt) was found in the adipose tissue of a man who worked in zone A for 6 months during the reclamation (1976–1977) and who died from lung cancer in 1989 (*23*).

Early and Mid-Term Health Effects

Several outcomes were examined (*24,25*), particularly in selected groups such as people from zone A and subjects with chloracne. Chloracne cases (193 subjects) were followed up to 1985. Biochemical indicators of hepatic function, total cholesterol and serum triglycerides, and nerve conduction tests were repeatedly performed. Compared with a control group, no significant differences and temporal trends in mean values of liver enzymes and lipids were detected. There were no motor and sensory nerve conduction differences between the two groups (*26*).

Clinical and electrophysiologic signs of peripheral neuropathy were examined in 1977 and 1978 in over 300 persons evacuated from zone A and compared to those of a nonexposed population. No increased frequency of overt cases of peripheral neuropathy was found, although the subgroup of subjects who had chloracne or elevated hepatic enzymes showed a 3-fold increased frequency of some clinical and electrophysiologic signs of peripheral neuropathy (*27*). A follow-up was conducted until 1983 of 153 subjects with chloracne and 123 control subjects. Signs of peripheral nervous system involvement were more frequent among exposed subjects, but none of the subjects met the diagnostic criteria for peripheral neuropathy (*28*).

TCDD was known to induce microsomal enzymes in the liver of animals (*29*). Liver enzyme induction was studied measuring urinary D-glucaric acid in various groups of adults and children from the contaminated and noncontaminated areas at different times between 1976 and 1981. Immediately after the accident 14 children with chloracne from zone A showed higher levels of urinary D-glucaric acid that returned to normal values in 1980. In 1981 two groups of children still had significantly elevated levels: those from a zone R sector close to the plant (the suburb called Polo; 62 subjects) and those from zone B (61 subjects) (*30*).

Immunologic effects of TCDD were investigated between 1976 and 1979 in 48 nonexposed children and 48 children from zone A. Results of tests performed showed higher levels of complement activity, higher values for lymphocyte responses to phytohemagglutinin and pokeweed mitogen, and increased numbers of peripheral lymphocytes among exposed children. Test design limitations and poor compliance of reference children made interpretation difficult (*31*).

Fifteen hundred children from the three contaminated areas (A, B, and R) were studied from 1976 to 1982 to determine whether liver function and lipid metabolism were affected as a consequence of TCDD exposure. Sixty-nine children from zone A showed increased γ-glutamyltranspeptidase and alanine aminotransferase activity in 1976 and 1977. However, the increase was within the reference limits and disappeared with time. No alterations in cholesterol and triglycerides were detected (*32*).

Ascertaining the incidence of spontaneous abortion among exposed subjects was complicated by problems such as the absence of a valid ongoing data collection system, moral and political issues related to legalization of abortion, and an active birth control campaign that may have dramatically decreased conception rates. All of these factors may have affected the completeness and the accuracy of data. Nonetheless, several attempts were made to evaluate the possible increased risk of spontaneous abortions by using different sources of information (medical statistics, physicians' notifications to county medical officers, hospital admission and discharge forms), but the results were inconclusive (*33,34*).

Comparison of cytogenetic findings on induced abortions in 19 exposed and 16 nonexposed women yielded inconclusive results (*35*). A higher frequency of chromosomal aberration in fetal tissue from TCDD-exposed women was found, but potential problems with variability in the cell culture process were noted. Another cytogenetic study evaluated chromosomal aberration in lymphocytes of 145 residents of zone A, 69 workers employed in the plant where the accident occurred, and 87 controls. No consistent evidence emerged of chromosomal effects associated with TCDD exposure (*36*).

The presence of congenital anomalies was evaluated in 34 subjects—30 with

induced abortions and 4 with spontaneous abortions. Direct examination and histologic studies of the embryos failed to demonstrate any gross developmental abnormalities (*37*). At the beginning of 1977 a congenital malformation registry was established that listed all live and still births (about 15,000) to women residing in the area. Infants born between 1977 and 1982 were examined for the presence of congenital malformations. Results failed to show an increased risk for birth defects (*38*).

A change in the sex ratio, with an excess of female offspring, was observed between 1977 and 1984 among children born to parents with high TCDD serum concentrations in 1976. Possible explanations for this change are dioxin-related modifications of the hormonal balance or an effect on genes controlling gender (*39*).

Long-Term Studies

Mortality and cancer incidence appear to be the only end points feasible to investigate and evaluate possible long-term effects of exposure to dioxin (*25*).

The A, B, and R zones included part of the territories of two health districts of the Lombardy region. All persons residing in the districts from the date of the accident onward were enrolled in the study. Those living in the three contaminated zones were considered exposed. Those living in the surrounding uncontaminated territory became the referent population; they shared the characteristic social and cultural habits and living and occupational backgrounds with the exposed population (*40*).

The follow-up of all study subjects (exposed and referent) was carried out with exposure status blinded and using the same criteria and methods during the same time span. Information from local population registries was the basis on which subjects were assigned to one of the exposure zones or the referent area. These registries are maintained by every city and locality in Italy and cover the whole nation. Individual changes of residence are systematically updated, which allows tracing of those who have left the study area (with 99.1% success). Once a person was located their vital status was available; in case of death the date and place of death and a detailed description of the cause of death reported to the National Statistics Institute was obtained (*41,42*). For the cancer incidence study, linking information on all hospitalization in the Lombardy region (nearly 9 million inhabitants) with the records of cohort members allowed identification of study subjects admitted or discharged with diagnoses mentioning or suggesting cancer. Original medical records were reexamined by experienced physicians to ascertain the correct diagnosis and the date of occurrence (first diagnosis) of cancer. The ascertainment rate for cancer morbidity was estimated with an ad hoc investigation in the two main hospitals of the study area (Desio and Seregno). All hospital records reporting a diagnosis of cancer during a 1.5-year period were compared with records obtained from the regional files of discharge diagnoses. The proportion of nondetected cases for malignancies ranged from 2.6 to 6.8% (*43*).

Comparison of long-term effects (mortality and cancer incidence) for the exposed and reference populations was performed by estimating relative risk(s) (RR) and their confidence interval(s) (CI) using Poisson regression models. The study population is shown in Table 3. Results in the 15-year period following the accident are summarized in Tables 4, 5, and 6.

The mortality rate for death from all causes did not differ appreciably in any of the three TCDD-contaminated zones from that for the reference population; however, unusual occurrences were observed for some specific causes.

For nonmalignant causes the clearest suggestions of unusual mortality were in zone A, the most heavily contaminated area (Table 4). Males had an increased mortality from cardiovascular disease, particularly from chronic ischemic heart disease (CIHD), and females from chronic rheumatic heart disease and hypertension. Excess mortality was observed for males with respiratory tract conditions, mainly chronic obstructive pulmonary disease (COPD). Diabetes mellitus exhibited a suggestive though nonsignificant increase in mortality among females. In zone A, cancer deaths are too few to draw any conclusions. Yet among females elevated mortality appeared to be associated with digestive sites.

Table 5 reports results for zone B. Among cardiovascular causes a modest nonsignificant increase was seen for CIHD. COPD showed significant excess mortality among females. Diabetes deaths were slightly elevated in males and significantly above expectations in females. Cancer mortality excesses were noted at some digestive and lymphohemopoietic sites. Among males a nearly 3-fold significant increase was seen for rectal cancer. No excesses were observed at other sites. Analysis by years since the accident showed an increased mortality from stomach and liver cancer among women after 10 years (5 deaths; RR, 2.4; 95% CI, 1.0–6.0 and 2 deaths; RR, 3.2; 95% CI, 0.8–13.2, respectively). Lymphohemopoietic neoplasms showed a statistically significant excess for leukemias among males, whereas females exhibited a 6-fold elevated RR for Hodgkin's disease and myeloma.

Results in zone R are reported in Table 6. Mortalities from CIHD were significantly elevated among both males and females; mortalities from hypertension were elevated among females. No increase in deaths from respiratory causes was noted. Mortality rates by specific cancer sites were, in general, similar to those of the reference population with few exceptions. Increased risks were found among males for soft-tissue sarcoma and esophageal cancer.

Discussion

Examination of the early and mid-term effects of TCDD exposure was not simple in the complex postaccident situation (*24*). Hectic conditions in the study area jeopardized the validity of many investigations no matter how carefully they were conducted. Selective participation, lack of reference data, and limited standardization of methods and performance of tests were common problems that contributed in many cases to inconclusive results (*9,25*). There is no doubt, however, that chloracne was attributable to accidental exposure to TCDD because of the nature of the lesion, its absolute frequency, and its distribution.

Long-term studies designed later were less affected by the above-mentioned constraints. Nevertheless, they had other types of inherent limitations; for example, the

Table 3. Number of subjects and results of follow-up studies, 1976 to 1991, in the Seveso study population.

Contamination zone	Total subjects, no.	Not traced, no. (%)	Person-years, no.	
			Males	Females
A	805	7 (0.9)	5541	5975
B	5943	53 (0.9)	42,219	41,391
R	38,625	361 (0.9)	265,408	271,483
Reference	232,747	2066 (0.9)	1,536,724	1,622,631

Table 4. Mortality, 1976 to 1991, among the population involved in the Seveso accident, zone A (high-exposure area).

Cause of death, *ICD-9* classification[a]	Males				Females			
	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI
All causes (000–999)	39	38.3	1.0	0.7–1.4	31	29.5	1.1	0.7–1.5
Diabetes (250)	0	0.6	–	–	2	1.1	1.8	0.4–7.0
All circulatory disease (390–459)	21	12.8	1.6	1.1–2.5	12	12.3	1.0	0.6–1.7
Chronic rheumatic heart disease (393–398)	0	0.1	–	–	3	0.2	15.8	5.0–50.8
Hypertension (400–405)	1	0.4	2.3	0.3–16.2	3	0.8	3.6	1.1–11.0
Ischemic heart disease (410–414)	9	6.0	1.5	0.8–2.8	1	3.7	0.3	0.0–2.0
Acute myocardial infarction (410)	4	4.3	0.9	0.3–2.5	1	1.8	0.6	0.1–4.0
Chronic ischemic heart disease (412, 414)	5	1.6	3.0	1.2–7.3	0	2.4	–	–
Other heart diseases (420–429)	3	1.7	1.8	0.6–5.5	3	2.2	1.4	0.4–4.3
Cerebrovascular disease (430–438)	5	3.3	1.5	0.6–3.7	2	4.1	0.5	0.1–2.0
Respiratory disease (460–519)	5	2.1	2.4	1.0–5.7	2	1.5	1.3	0.3–5.3
Chronic obstructive pulmonary disease (490–493)	4	1.1	3.7	1.4–9.8	1	0.5	2.1	0.3–14.9
Digestive disease (520–579)	2	3.1	0.7	0.2–2.6	2	1.6	1.2	0.3–5.0
All cancers (140-208)	6	13.5	0.4	0.2–1.0	10	8.5	1.2	0.6–2.2
Stomach (151)	0	1.8	–	–	1	1.1	0.9	0.1–6.7
Colon (153)	0	0.8	–	–	2	0.8	2.6	0.6–10.5
Pancreas (157)	1	0.5	1.9	0.3–13.5	0	0.3	–	–
Other digestive (159)	0	0.2	–	–	2	0.2	8.1	2.0–32.8
Lung (162)	4	4.2	1.0	0.4–2.6	0	0.5	–	–
Melanoma (172)	0	0.1	–	–	1	0.1	9.4	1.3–68.8
Breast (174)	0	0.0	–	–	1	1.8	0.6	0.1–3.9
Ovary (183)	–	–	–	–	1	0.4	2.3	0.3–16.5
Prostate (185)	0	0.7	–	–	–	–	–	–
Bladder (188)	1	0.4	2.4	0.3–16.8	0	0.1	–	–

[a] *ICD-9* classifications are in parentheses. Abbreviations: Exp, expected deaths; *ICD-9, International Classification of Diseases, Ninth Revision* (World Health Organization, Geneva); Obs, observed deaths.

Table 5. Mortality, 1976 to 1991, among the population involved in the Seveso accident, zone B (medium-exposure area).

Cause of death, *ICD-9* classification[a]	Males				Females			
	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI
All causes (000–999)	275	288.4	1.0	0.8–1.1	193	193.8	1.0	0.9–1.1
Diabetes (250)	6	4.9	1.2	0.5–2.7	13	7.4	1.8	1.0–3.0
All circulatory disease (390–459)	94	100.7	0.9	0.8–1.1	79	80.6	1.0	0.8–1.2
Chronic ischemic heart disease (412, 414)	18	13.9	1.3	0.8–2.1	16	12.5	1.3	0.8–2.1
Respiratory disease (460–519)	13	18.2	0.7	0.4–1.2	10	10.0	1.0	0.5–1.9
Chronic obstructive pulmonary disease (490–493)	9	9.3	1.0	0.5–1.9	8	3.2	2.5	1.2–5.0
Digestive disease (520–579)	15	20.8	0.7	0.4–1.2	13	10.3	1.3	0.7–2.2
All cancers (140–208)	104	93.8	1.1	0.9–1.3	48	54.2	0.9	0.7–1.2
Digestive (150–159)	33	35.6	0.9	0.6–1.3	18	21.3	0.8	0.5–1.3
Esophagus (150)	1	2.7	0.4	0.1–2.6	0	0.6	–	–
Stomach (151)	10	12.1	0.8	0.4–1.5	7	6.8	1.0	0.5–2.2
Colon (153)	5	6.0	0.8	0.3–2.0	3	4.9	0.6	0.2–1.9
Rectum (154)	7	2.4	2.9	1.3–6.2	2	1.6	1.3	0.3–5.1
Hepatobiliary (155–156)	4	7.2	0.6	0.2–1.5	4	3.5	1.1	0.4–3.1
Liver (155)	4	6.5	0.6	0.2–1.7	3	2.3	1.3	0.4–4.1
Pancreas (157)	2	3.6	0.6	0.1–2.2	1	1.8	0.5	0.1–3.9
Respiratory (160–165)	40	32.0	1.2	0.9–1.7	2	4.0	0.5	0.1–2.0
Lung (162)	34	27.6	1.2	0.9–1.7	2	3.5	0.6	0.1–2.3
Bone (170)	0	0.6	–	–	1	0.4	2.6	0.3–19.4
Soft-tissue sarcoma (171)	0	0.3	–	–	0	0.2	–	–
Melanoma (172)	0	0.4	–	–	0	0.7	–	–
Breast (174)	0	0.1	–	–	9	11.4	0.8	0.4–1.5
Genitourinary tract (179–189)	10	10.5	1.0	0.5–1.8	5	7.7	0.6	0.3–1.6
Uterus (179–182)	–	–	–	–	1	3.0	0.3	0.0–2.4
Ovary (183)	–	–	–	–	0	2.7	–	–
Prostate (185)	6	4.8	1.2	0.6–2.8	–	–	–	–
Bladder (188)	3	3.2	0.9	0.3–3.0	0	0.9	–	–
Brain (191)	1	1.3	0.8	0.1–5.5	3	0.9	3.2	1.0–10.3
Thyroid gland (193)	1	0.2	4.9	0.6–39.0	1	0.3	3.2	0.4–24.5
Lymphohemopoietic (200–208)	12	5.1	2.4	1.3–4.2	7	3.9	1.8	0.8–3.8
Hodgkin's (201)	2	0.6	3.3	0.8–14.0	2	0.3	6.5	1.5–29.0
Non-Hodgkin's (200, 202)	2	1.4	1.5	0.4–6.0	0	1.2	–	–
Myeloma (203)	1	0.9	1.1	0.2–8.2	4	0.6	6.6	2.3–18.5
Leukemia (204–208)	7	2.2	3.1	1.4–6.7	1	1.8	0.6	0.1–4.0
Lymphatic (204)	2	0.7	2.9	0.7–12.3	0	0.5	–	–
Myeloid (205)	3	0.9	3.3	1.0–10.6	0	0.1	–	–

[a] *ICD-9* classifications are in parentheses.

Table 6. Mortality, 1976 to 1991, among the population involved in the Seveso accident, zone R (low-exposure area).

Cause of death, *ICD-9* classification[a]	Males				Females			
	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI
All causes (000–999)	2032	1964.0	1.0	1.0–1.1	1695	1617.0	1.0	1.0–1.1
Diabetes (250)	38	34.7	1.1	1.8–1.5	75	63.4	1.2	0.9–1.5
All circulatory disease (390–459)	755	684.7	1.1	1.0–1.2	797	701.2	1.1	1.0–1.2
Chronic ischemic heart disease (412, 414)	133	93.7	1.4	1.2–1.7	141	111.0	1.3	1.1–1.5
Hypertension (400–405)	34	25.3	1.3	0.9–1.9	74	48.3	1.5	1.2–2.0
Respiratory disease (460–519)	133	122.0	1.1	0.9–1.3	84	87.7	1.0	0.8–1.2
Chronic obstructive pulmonary disease (490–493)	74	63.0	1.2	0.9–1.5	37	28.1	1.3	0.9–1.9
Digestive disease (520–571)	165	144.3	1.1	1.0–1.3	89	83.6	1.1	0.8–1.3
All cancers (140–208)	607	654.5	0.9	0.9–1.0	401	435.2	0.9	0.8–1.0
Digestive (150–159)	226	249.2	0.9	0.8–1.0	158	177.5	0.9	0.8–1.0
Esophagus (150)	30	18.9	1.6	1.1–2.4	5	5.4	0.9	0.4–2.4
Stomach (151)	76	85.0	0.9	0.7–1.1	58	57.4	1.0	0.8–1.3
Colon (153)	34	41.4	0.8	0.6–1.2	33	40.9	0.8	0.6–1.2
Rectum (154)	19	16.8	1.1	0.7–1.8	12	12.9	0.9	0.5–1.7
Hepatobiliary (155–156)	35	50.4	0.7	0.5–1.0	25	29.4	0.8	0.6–1.3
Liver (155)	31	45.8	0.7	0.5–1.0	12	19.6	0.6	0.3–1.1
Pancreas (157)	20	25.3	0.8	0.5–1.3	11	15.1	0.7	0.4–1.4
Other digestive (159)	6	8.6	0.7	0.3–1.6	11	13.4	0.8	0.4–1.5
Respiratory (160–165)	208	225.2	0.9	0.8–1.1	35	32.2	1.1	0.8–1.5
Lung (162)	176	194.4	0.9	0.8–1.1	29	27.7	1.0	0.7–1.6
Bone (170)	2	4.2	0.5	0.1–2.0	7	2.9	2.4	1.0–5.7
Soft-tissue sarcoma (171)	4	1.9	2.1	0.7–6.5	0	1.5	–	–
Melanoma (172)	3	2.8	1.1	0.3–3.7	3	5.0	0.6	0.2–2.0
Breast (174)	0	0.6	–	–	67	88.6	0.8	0.6–1.0
Genitourinary tract (179–189)	73	72.3	1.0	0.8–1.3	65	61.0	1.1	0.8–1.4
Uterus (179–182)	–	–	–	–	27	23.7	1.1	0.8–1.7
Ovary (183)	–	–	–	–	21	20.7	1.0	0.6–1.6
Prostate (185)	39	33.0	1.2	0.8–1.7	–	–	–	–
Bladder (188)	21	22.1	0.9	0.6–1.5	4	6.2	0.6	0.2–1.8
Brain (191)	12	9.0	1.3	0.7–2.5	8	7.2	1.1	0.5–2.4
Thyroid gland (193)	0	1.5	–	–	2	2.4	0.8	0.2–3.6
Lymphohemopoietic (200–208)	27	34.8	0.8	0.5–1.2	29	30.5	1.0	0.6–1.4
Hodgkin's (201)	0	4.0	–	–	4	2.1	1.9	0.6–5.8
Non-Hodgkin's (200, 202)	10	9.4	1.1	0.5–2.1	8	9.3	0.9	0.4–1.8
Myeloma (203)	5	6.3	0.8	0.3–2.0	5	5.1	1.0	0.4–2.5
Leukemia (204–208)	12	15.1	0.8	0.4–1.5	12	13.9	0.9	0.5–1.6
Lymphatic (204)	6	4.5	1.3	0.5–3.2	3	3.9	0.8	0.2–2.6
Myeloid (205)	4	6.3	0.6	0.2–1.8	4	6.9	0.6	0.2–1.6

[a] *ICD-9* classifications are in parentheses.

restricted number of individual exposure measurements, the relatively short period (15 years) elapsed since exposure, and the small size of the population in the most polluted area. These limitations should be borne in mind when evaluating results from any of these studies.

The cardiovascular excess mortality noted might be related both to the accident experience with its burden of psychosocial stressors and the exposure to TCDD. The former could have precipitated early deaths among persons with preexisting ill health conditions (*44*). This hypothesis is supported by the early postaccident occurrence of the deaths, the advanced age of some of the affected people, and the prevailing chronic type of cardiovascular disorders (*40*). TCDD alters lipid metabolism, cardiac function, and morphology in experimental studies with animals (*45–52*), although data for humans are still inconclusive (*53*).

Increased respiratory disease mortality can reasonably be linked to the same determining factors (psychosocial and chemical) hypothesized for cardiovascular deaths. Here, again, early deaths among persons with impaired respiratory systems may have been caused by the social and emotional impact of the disaster (*44*). In addition, the immunotoxic action of dioxin may have impaired defense mechanisms that usually protect against respiratory infection episodes, which play major roles in the natural history of COPD (*54*). The possible role of smoking as a confounding factor, if even present, cannot explain the high RR values for these causes. In fact, the index and reference populations were closely comparable with regard to this factor (*42*), and smoking-related cancers were not increased among the exposed population. Few other epidemiologic studies addressed the association of TCDD exposure and respiratory nonmalignant disease, and those that did so failed to uncover any increased risk (*55*).

Findings about diabetes, although merely suggestive, warrant attention in light of the results of investigations on other dioxin-exposed populations (*56,57*).

Results of experimental and epidemiologic studies, along with mechanistic knowledge on dioxin toxicity, support the hypotheses that dioxin is carcinogenic to humans (*58*). In the Seveso study the most consistently suggestive pattern of increased cancer risk was seen among people living in zone B where the possible accident-related cancer effects were a priori expected to appear because of the high exposure level and the fairly large population size. Cancer incidence results, presently available for the period 1977 to 1986 (*43*), support the 1976 to 1991 mortality findings of an increased occurrence of digestive and

lymphohemopoietic cancer among residents of zone B (although inconsistencies about the specific sites affected exist) and of soft-tissue sarcoma in zone R (the least contaminated but the most populated exposure zone). Previous epidemiologic studies of TCDD-exposed populations lent partial support to the Seveso findings. A dose-dependent increase of digestive cancer was noted in a cohort of German workers accidentally exposed to TCDD (*59*) but not in other exposed populations (*58*). Several studies of chemical workers have confirmed the increased occurrence of lymphohemopoietic tissue neoplasms after exposure to TCDD (*60–63*). Soft-tissue sarcomas have been repeatedly associated with dioxin exposure (*64,65*). Some of the discrepancies among the studies could be explained by differences in exposure levels, concomitant exposure to other chemicals, and lengths of observation periods.

The results reported and discussed in this paper do not provide conclusive evidence of long-term effects on the exposed subjects of the Seveso accident. For this reason the follow-up period for the mortality and cancer incidence studies has been extended and molecular epidemiology studies (*66*) have been initiated. These will probably contribute to bridging the existing gap in knowledge about human toxicity of TCDD and about long-term sequelae on human health of the Seveso accident.

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